Bleeding patterns in patients before and after diagnosis of von Willebrand disease: Analysis of a US medical claims database

Robert Sidonio Jr, *Emory University*
Jonathan C Roberts, *Bleeding & Clotting Disorders Inst*
Lynn M Malec, *Versiti Blood Center of Wisconsin*
Imrran Halari, *Charles River Associates, Boston Massachusetts*
Sarah A Hale, *Baxalta US Inc*
Abiola Oladapo, *Baxalta US Inc*
Robert F Sidonio, *Emory University*

Journal Title: HAEMOPHILIA

Volume: Volume 28, Number 1

Publisher: WILEY | 2021-11-10, Pages 97-108

Type of Work: Article | Final Publisher PDF

Publisher DOI: 10.1111/hae.14448

Permanent URL: https://pid.emory.edu/ark:/25593/w1scv

Final published version: http://dx.doi.org/10.1111/hae.14448

Copyright information:

Received: 1 April 2021 | Revised: 2 September 2021 | Accepted: 17 October 2021

DOI: 10.1111/hae.14448

Haemophilia WILEY

ORIGINAL ARTICLE

Von Willebrand disease

Bleeding patterns in patients before and after diagnosis of von Willebrand disease: Analysis of a US medical claims database

Jonathan C. Roberts[1] | Lynn M. Malec[2] | Imrran Halari[3] | Sarah A. Hale[4] | Abiola Oladapo[4] | Robert F. Sidonio Jr[5]

[1] Bleeding & Clotting Disorders Institute, Peoria, Illinois, USA

[2] Versiti Blood Center of Wisconsin, Milwaukee, Wisconsin, USA

[3] Charles River Associates, Boston, Massachusetts, USA

[4] Baxalta US Inc., a, Takeda company, Cambridge, Massachusetts, USA

[5] Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Emory University, Atlanta, Georgia, USA

Correspondence
Jonathan C. Roberts, Bleeding & Clotting Disorders Institute, 427W. Northmoor Rd., Peoria, IL 61614, USA.
Email: jroberts@ilbcdi.org

Abstract

Introduction: Von Willebrand disease (VWD) is the most common inherited bleeding disorder. The bleeding phenotype is variable, and some individuals have persistent symptoms post-diagnosis.

Aim: To characterize bleeding patterns in patients with VWD before and after diagnosis.

Methods: De-identified claims data for commercially insured patients in the IQVIA PharMetrics® Plus US database (Jan-2006 to Jun-2015) were extracted. Eligible patients had ≥2 claims for VWD (ICD-9 code 286.4), and continuous health-plan enrolment for ≥2 years before and after diagnosis. Bleeding event, treatment and treating-physician type were analysed for 18 months before and 7-24 months after diagnosis, according to pre-diagnosis bleeding phenotype (claims from one vs multiple bleed sites) and post-diagnosis bleeding status (resolved [no post-diagnosis bleed claims] vs continued [≥1 claim]).

Results: Data for 3756 eligible patients (72.6% female; 71.0% aged ≥18 years at diagnosis) were analysed. Overall, 642 (17.1%) and 805 (21.4%) patients had single- and multiple-site bleed claims pre-diagnosis, respectively, and 1263 (33.6%) patients (38.5% of women, 20.8% of men) continued to bleed post-diagnosis. Multiple-site bleeding was associated with pre-diagnosis heavy menstrual bleeding (HMB), oral contraceptive (OC) use and nasal cauterization. Continued bleeding post-diagnosis was associated with pre-diagnosis gastrointestinal bleeding, HMB and epistaxis; pre-diagnosis use of OCs, aminocaproic acid and nasal cauterization; and younger age at diagnosis. Few patients consulted a haematologist for bleed management.

Conclusion: Many patients with VWD have persistent bleeding from multiple sites and continue to bleed post-diagnosis. Our findings suggest a need to optimize management to reduce the symptomatic burden of VWD following diagnosis.

KEYWORDS
database, diagnosis, epistaxis, gastrointestinal haemorrhage, menorrhagia, therapeutics, von Willebrand disease

1 | INTRODUCTION

Von Willebrand disease (VWD), the most common inherited bleeding disorder, is characterized by excessive mucocutaneous bleeding.[1,2] Symptoms can include ecchymosis, epistaxis, prolonged bleeding from minor wounds, heavy menstrual bleeding (HMB), oral bleeding and bleeding after surgery or childbirth.[1,2] It is estimated that .01% to .1% of the population has clinically relevant VWD symptoms.[3,4] However, bleeding severity varies widely and is poorly defined despite its importance in treatment decisions.[5–8]

VWD remains underrecognized and underdiagnosed owing to a lack of awareness, heterogeneity of phenotypes and the need for repeated, complex diagnostic tests,[9–12] and there may be a significant number of patients with symptomatic but undiagnosed VWD.[13] There is a need to optimize VWD management, particularly for difficult bleed types such as HMB and gastrointestinal (GI) bleeding.[10,14–16] Up to one-third of female and one-fifth of male patients may experience continued bleeding in the year after diagnosis, which can affect quality of life and healthcare utilization, especially if there are comorbidities such as anaemia.[17–20]

The objective of the current analysis was to characterize bleeding patterns in patients with VWD before and after diagnosis and identify characteristics of those who continued to bleed following diagnosis compared with those in whom bleeding resolved. Additionally, bleeding and treatment patterns were evaluated in patients with bleeding from a single site, compared with those with bleeding from multiple sites.

2 | MATERIALS AND METHODS

This was a longitudinal retrospective analysis of de-identified healthcare claims information from commercially insured patients in the IQVIA PharMetrics Plus US database between January 2006 and June 2015. The IQVIA PharMetrics® Plus US database consists of fully adjudicated medical and pharmacy claims. It contains a longitudinal view of inpatient and outpatient services, prescription and office/outpatient administered drugs, cost and enrolment information. An enrolled patient can be tracked across all sites of care.

Patients eligible for analysis had ≥2 insurance claims for VWD (ICD-9 code 286.4, of which the first claim was designated as the date of diagnosis), and continuous health-plan enrolment for ≥2 years before, and ≥2 years after, diagnosis. Exclusion criteria were a primary diagnosis for haemophilia A, qualitative platelet disorders or anticoagulant treatment. Ethical approval was not required because de-identified data were used.

The time periods analysed were the 18 months before diagnosis and from 7 to 24 months after diagnosis (the 6-month post-diagnosis period was omitted because initial analyses suggested treatments were still being optimized). Extracted data for eligible patients included demographics, bleed event types, specialty of the treating physician for bleed management visits (for inpatients, this was the admitting physician only) and type of VWD treatment. Extracted bleed claims were for menorrhagia (ICD-9 claim codes 626.2, 626.3, 626.4, 626.6, 626.8, 626.9, 627.0, 627.1, 627.4), post-partum bleeding (666.x), epistaxis (784.7, 21.0x, R04.0), prolonged bleeding (790.92), GI bleeds (578.9, 578.x), gum bleeds (523.8), joint bleeds (719.1x), haemorrhage complicating a delivery (641.9), bleeding complicating a procedure (998.11), coagulation defects complicating pregnancy, childbirth or the puerperium (649.3x), haemorrhage unspecified (459.0) and other bleeds (641.3x, 287.5, 287.4x, 287.3x, 782.7). Claims for anaemia (codes 280.xx and 285.xx) were documented. Information on VWD subtype was not available.

Bleeding phenotype was defined as multiple-site (≥2 types of bleed claim) or single site (one type of bleed claim) bleeding before VWD diagnosis. Bleeding status was defined as continued bleeding (≥1 post-diagnosis bleed claim) or resolved bleeding (no post-diagnosis bleed claims). Extracted data were analysed according to pre-diagnosis bleeding phenotype, post-diagnosis bleeding status and sex. The t-test was used to compare mean age at VWD diagnosis, and the Chi-square test to compare occurrence of pre-diagnosis bleed type claims and pre- and post-diagnosis claims for treatment types, by bleeding status and phenotype. Multiple logistic regression analysis was conducted to evaluate associations of pre-diagnostic bleed types, and pre- and post-diagnosis treatments, with bleeding phenotype and status, and of post-diagnosis treatments with post-diagnosis bleed types. Age (exact), sex and haematologist visit history were included in the model as control variables. All analyses were conducted using SAS software version 9.4.

3 | RESULTS

3.1 | Patient population

Overall, 3756 patients met the inclusion criteria, of whom 72.6% were female and 71.0% were adults (≥18 years) at VWD diagnosis (Figure 1). Overall, 1707 (45.4%) patients had ≥1 bleed claims during the 18-month pre-VWD diagnosis analysis period. Pre-diagnosis bleeding phenotype could be assigned for 1447 patients: 642 patients (17.1% of total population) had single bleed sites, and 805 (21.4%) had multiple bleed sites. Women comprised a slightly higher proportion of the single-bleed-site (76.2%) than the multiple-bleed-site (67.3%) group (Figure 1).

Post-diagnosis, 2493/3756 (66.4%) patients had resolved bleeding (excluding claims for maintenance visits), while 1263 (33.6%) patients (38.5% of female and 20.8% of male patients) had continued bleeding. Women comprised 83.1% of the continued-bleeding group, and 67.3% of the resolved-bleeding group.

3.2 | Age at VWD diagnosis

Mean age at VWD diagnosis was 34.3 (standard deviation [SD] 19.6) years (median [range] 34 [2–82] years). Among men and women combined, age at diagnosis was significantly lower among patients with multiple (vs single) bleed sites and with continued (vs resolved) bleeding (Table 1). These differences were also statistically significant among

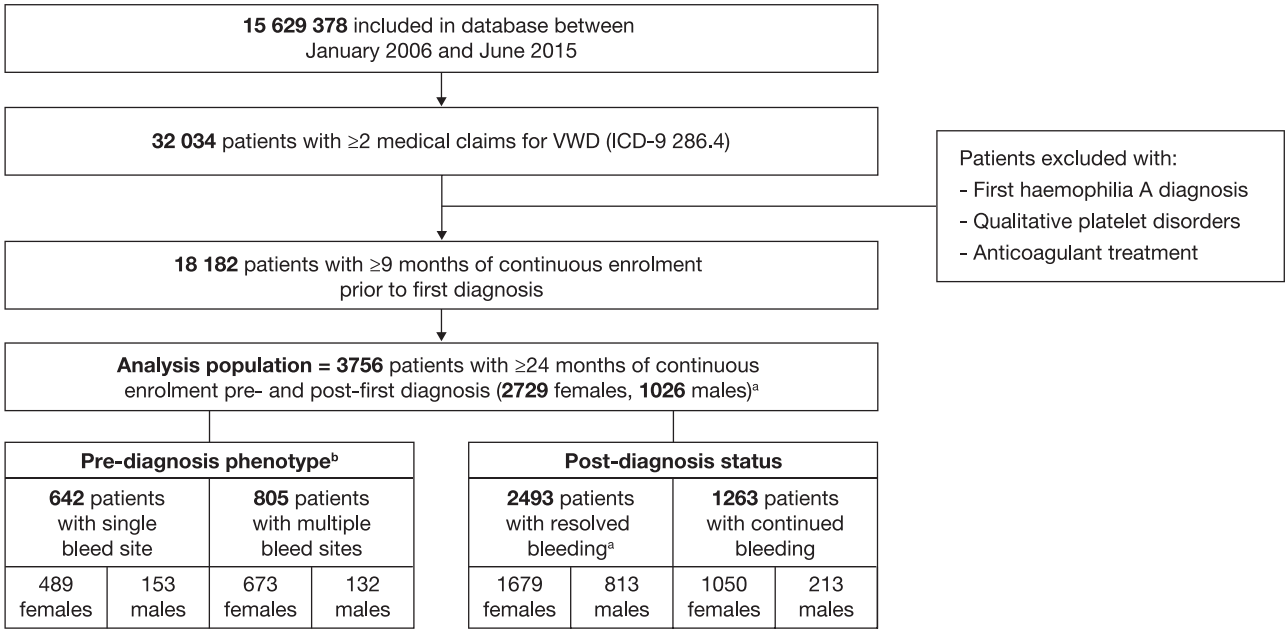

FIGURE 1 Derivation and characteristics of analysis population.
VWD, von Willebrand disease.
[a]One patient was missing data on sex.
[b]1447 of 1707 patients with bleeding event claims during the 18-month pre-VWD diagnosis period could be assigned a pre-diagnosis bleed phenotype. 'Single bleed sites' and 'multiple bleed sites' refer to patients with one type of bleed claim or at least two types of bleed claim in the pre-VWD diagnosis period, respectively. 'Resolved bleeding' and 'continued bleeding' refer to absence or presence of claims for bleeds in the post-VWD diagnosis period, respectively

TABLE 1 Comparison of mean age at diagnosis of von Willebrand disease according to sex, pre-diagnosis bleeding phenotype and post-diagnosis bleeding status

Patient population	Comparison	n	Mean (SD) age at VWD diagnosis (y)	*P*(t-test)
All patients (N = 3756)[a]	Male	1026	30.6 (21.9)	< .0001[b]
	Female	2727	35.7 (18.5)	
Patients with bleed claims and an ascertainable bleed phenotype in the 18 months pre-diagnosis (n = 1447)	Single bleed site	642	32.1 (19.0)	.0107[b]
	Multiple bleed sites	805	29.8 (17.7)	
All patients (N = 3756)[a]	Resolved bleeding	2491	35.2 (20.1)	< .0001[b]
	Continued bleeding	1262	32.5 (18.4)	
Resolved bleeding (n = 2493)[a]	Male	813	30.9 (21.6)	< .0001[b]
	Female	1678	37.3 (19.0)	
Continued bleeding (n = 1263)[a]	Male	213	29.2 (22.9)	.0096[b]
	Female	1049	33.1 (17.3)	
Single bleed sites (n = 642)	Male	153	26.1 (20.8)	< .0001[b]
	Female	489	34.0 (18.0)	
Multiple bleed sites (n = 805)	Male	132	27.5 (24.0)	.0986
	Female	673	30.3 (16.1)	

SD, standard deviation; VWD, von Willebrand disease.
[a]Two patients were missing data on age, and one patient on sex.
[b]Statistically significant ($P < .05$). 'Resolved bleeding' and 'continued bleeding' refer to absence or presence of claims for bleeds in the post-VWD diagnosis period, respectively. 'Single bleed sites' and 'multiple bleed sites' refer to patients with one type of bleed claim or at least two types of bleed claim in the pre-VWD diagnosis period, respectively.

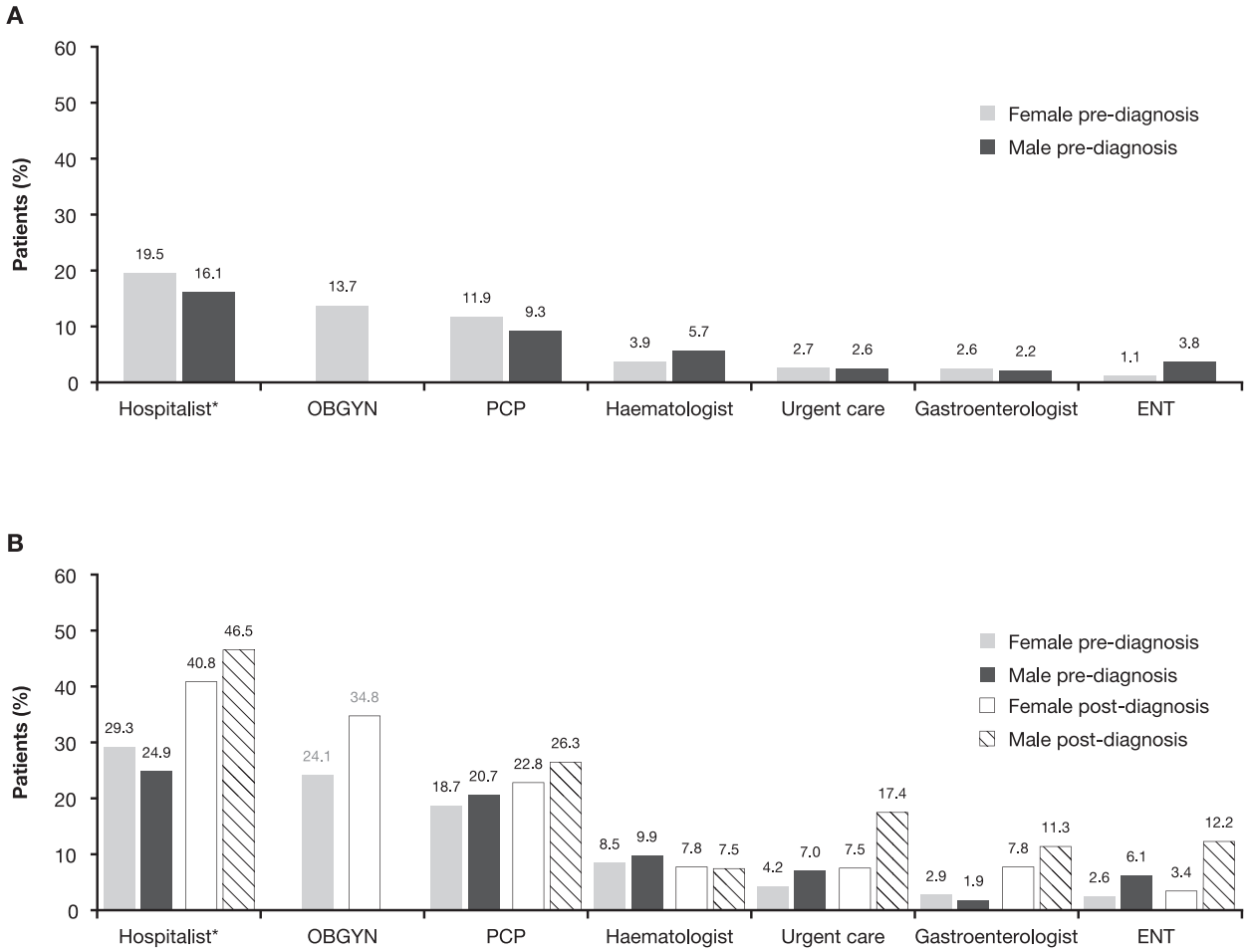

FIGURE 2 Most common specialties of treating physicians for bleed claims. (A) Patients with resolved bleeding. (B) Patients with continued bleeding.
ENT, ear, nose and throat specialist; OBGYN, obstetrician-gynaecologist; PCP, primary care physician.
Data are percentage of patients visiting the physician specialty for a bleed claim; specialties visited by > 1% of patients are included.
[a]'Hospitalist' category may have included haematologists. Data shown include visits to a specialist to address a bleed

women ($P = .0002$, multiple- vs single site bleeding; $P < .0001$, continued vs resolved bleeding), but not men ($P > .05$ for each comparison). Mean (SD) age at diagnosis was significantly lower for men than women, both in the overall population and among patients with single site, resolved and continued bleeding.

3.3 | Treating physician specialty

Overall, hospital medicine specialists (hospitalists) were most commonly consulted for a bleeding event in both the pre- and post-diagnosis periods (with visits from 21.8% and 14.0% of patients, respectively), followed by primary care physicians (PCPs; 13.7% and 7.9%, respectively) and obstetrician-gynaecologists (OBGYNs; 12.9% and 9.7%, respectively). Haematologist visits for bleeding events were documented for only 5.9% of patients before diagnosis and 2.6% after diagnosis.

The most common physicians consulted for women were hospitalists, OBGYNs and PCPs, for both pre-diagnosis bleeds in patients whose bleeding resolved (Figure 2A) and pre- and post-diagnosis bleeds in those with continued bleeding (Figure 2B). For men with resolved or continued bleeding, the most common physician types consulted for pre-diagnosis bleeds were hospitalists, PCPs and haematologists (Figure 2A, 2B), compared with hospitalists, PCPs and urgent-care physicians for post-diagnosis bleeds in patients with continued bleeding (Figure 2B). Thus, more men with continued bleeding interacted with urgent-care physicians post-diagnosis compared with pre-diagnosis.

3.4 | Bleeding patterns and anaemia

Overall, bleed claims reduced following VWD diagnosis: 45.4% and 33.6% of patients had bleed claims during the pre- and post-diagnosis periods, respectively. In total, 59% of patients (61% of women and 49% of men) with continued bleeding had bleed-related claims before diagnosis compared with 38% (41% of women and 32% of men) whose bleeding subsequently resolved.

TABLE 2 Bleed type frequency and treatment use according to post-diagnosis bleeding status and pre-diagnosis bleeding phenotype

	Bleeding phenotype before VWD diagnosis			Bleeding status after VWD diagnosis		
	Single bleed site (n = 642)	Multiple bleed site (n = 805)	*P* (Chi-square test)	Continued (n = 1263)	Resolved (n = 2493)	*P* (Chi-square test)
Bleed type before VWD diagnosis, n (%)						
Gastrointestinal bleed	71 (11.1)	80 (9.9)	.4882	67 (5.3)	84 (3.4)	.0043[a]
Heavy menstrual bleeding	261 (40.7)	521 (64.7)	< .0001[a]	410 (32.5)	372 (14.9)	< .0001[a]
Mucosal bleed	60 (9.3)	77 (9.6)	.8874	51 (4.0)	86 (3.4)	.3635
Epistaxis	127 (19.8)	166 (20.6)	.6931	132 (10.5)	161 (6.5)	< .0001[a]
Coagulation defects complicating pregnancy, childbirth or puerperium	22 (3.4)	12 (1.5)	.0157[a]	17 (1.3)	17 (.7)	.0423[a]
Haemorrhage unspecified	139 (21.7)	150 (18.6)	.1537	107 (8.5)	182 (7.3)	.2031
Treatment type before VWD diagnosis						
Oral contraceptives[b]	98 (20.0)	188 (27.9)	.002[a]	238 (22.7)	244 (14.5)	< .0001[a]
Desmopressin	31 (4.8)	52 (6.5)	.185	74 (5.9)	118 (4.7)	.1389
Von Willebrand factor	12 (1.9)	8 (1.0)	.1565	15 (1.2)	30 (1.2)	.9666
Aminocaproic acid	23 (3.6)	21 (2.6)	.2838	37 (2.9)	50 (2.0)	.0753
Nasal cauterization	26 (4.0)	48 (6.0)	.1008	35 (2.8)	42 (1.7)	.0264[a]
Treatment type after VWD diagnosis						
Oral contraceptives[b]	107 (21.9)	182 (27.0)	.0445[a]	303 (28.9)	251 (15.0)	< .0001[a]
Desmopressin	59 (9.2)	122 (15.2)	.0007[a]	176 (13.9)	202 (8.1)	< .0001[a]
Von Willebrand factor	22 (3.4)	19 (2.4)	.2245	63 (5.0)	40 (1.6)	< .0001[a]
Aminocaproic acid	30 (4.7)	67 (8.3)	.0058[a]	90 (7.1)	112 (4.5)	.0007[a]
Nasal cauterization	12 (1.9)	21 (2.6)	.3492	56 (4.4)	1 (.0)	< .0001[a]

VWD, von Willebrand disease.

[a]Statistically significant ($P < .05$) for frequency in patients with continued bleeding compared with resolved bleeding, or in patients with multiple bleed sites compared with a single bleed site. 'Resolved bleeding' and 'continued bleeding' refer to absence or presence of claims for bleeds in the post-VWD diagnosis period, respectively. 'Single bleed sites' and 'multiple bleed sites' refer to patients with one type of bleed claim or at least two types of bleed claim in the pre-VWD diagnosis period, respectively.

[b]Oral contraceptive use was evaluated in female patients only (continued bleeding, n = 1050; resolved bleeding, n = 1679; single bleed site, n = 489; multiple bleed site, n = 673).

In total, 1420 (37.8%) patients (41.7% of women and 27.6% of men) had at least one claim for anaemia. Among both male and female patients with continued bleeding, the percentage of patients with an anaemia claim increased following VWD diagnosis (from 23% pre-diagnosis to 27% post-diagnosis in women, and from 15% to 20% in men). Among patients with resolved bleeding, the rate of anaemia claims decreased following diagnosis (from 18% to 14% in women, and 11% to 7% in men).

3.5 | Bleed types

Pre-diagnosis bleed claims for HMB, but not other bleed types, were significantly more common among women with multiple (compared with single) bleed sites (Table 2). Conversely, coagulation defects complicating pregnancy, childbirth or the puerperium were significantly more common among patients with a single (vs multiple) bleed site (Table 2). HMB was positively associated with a multiple-site bleeding, and coagulation defects complicating pregnancy, childbirth or the puerperium were negatively associated with multiple-site bleeding (Table 3).

Among women with resolved and continued bleeding, the most common pre-diagnosis bleed claims were for HMB, haemorrhage (unspecified) and epistaxis (Figure 3A, 3B). The most common bleeds in the post-diagnosis period for women with continued bleeding were HMB, GI bleeds and mucosal bleeds (Figure 3B). In men with resolved bleeding, the most common pre-diagnosis bleed claims were for epistaxis, haemorrhage (unspecified) and mucosal bleeds (Figure 3A). For men with continued bleeding, the most common pre-diagnosis bleed claims were for epistaxis, haemorrhage (unspecified) and GI bleeds compared with epistaxis, GI bleeds and haemorrhage (unspecified) in the post-diagnosis period (Figure 3B). Among both men and women with continued bleeding, the frequency of claims for the majority of bleed types increased from the pre- to post-diagnosis period (Figure 3B).

TABLE 3 Association of bleed types and treatments with post-diagnosis bleeding status and pre-diagnosis bleeding phenotype

	Multiple (vs single) bleed sites before VWD diagnosis		Continued (vs resolved) bleeding after VWD diagnosis	
	Odds ratio (95% CI)[a]	*P*	Odds ratio (95% CI)[b]	*P*
Bleed type before VWD diagnosis				
Gastrointestinal bleed	1.01 (.71–1.44)	.9397	1.71 (1.22–2.40)	.0019[c]
Heavy menstrual bleeding	2.87 (2.21-3.72)	< .0001[c]	2.07 (1.74–2.46)	< .0001[c]
Mucosal bleed	1.18 (.82–1.71)	.3693	1.27 (.88–1.82)	.2
Epistaxis	1.26 (.95–1.68)	.1055	1.97 (1.53–2.55)	< .0001[c]
Coagulation defects complicating pregnancy, childbirth or puerperium	.40 (.20–.82)	.0129[c]	1.64 (.83–3.26)	.1546
Haemorrhage unspecified	.87 (.66–1.14)	.2988	1.16 (.90-1.50)	.2534
Treatment type before VWD diagnosis				
Oral contraceptives[d]	1.41 (1.06–1.89)	.0193[c]	1.57 (1.28–1.93)	< .0001[c]
Desmopressin	1.37 (.86–2.17)	.1864	1.18 (.87–1.61)	.2828
Von Willebrand factor	.59 (.24–1.48)	.2621	1.09 (.57–2.07)	.7926
Aminocaproic acid	.72 (.39–1.33)	.2893	1.57 (1.01-2.45)	.0477[a]
Nasal cauterization	1.86 (1.12-3.07)	.0165[c]	2.07 (1.30-3.31)	.0024[a]
Treatment type after VWD diagnosis				
Oral contraceptives[d]	1.17 (.88–1.58)	.2848	2.21 (1.80-2.71)	< .0001[c]
Desmopressin	1.67 (1.20-2.33)	.0027[c]	1.66 (1.33–2.07)	< .0001[c]
Von Willebrand factor	.71 (.37–1.33)	.2783	3.44 (2.27–5.22)	< .0001[c]
Aminocaproic acid	1.73 (1.10-2.72)	.0177[c]	1.52 (1.13–2.04)	.006[c]
Nasal cauterization	1.65 (.80-3.41)	.1798	171.93 (23.61 to > 999.99)	< .0001[c,e]

CI, confidence interval; VWD, von Willebrand disease.
Multiple logistic regression analysis with age (exact), sex and haematologist visit history as control variables.
[a]If OR = 1, there is an equal likelihood of multiple or single site bleeding pre-diagnosis; if OR > 1, bleeding is more likely to be multiple-site, and if OR < 1, bleeding is more likely to be single site.
[b]If OR = 1, there is an equal likelihood of resolved or continued bleeding post-diagnosis; if OR > 1, bleeding is more likely to be continued, and if OR < 1, bleeding is more likely to be resolved.
[c]Significant association between bleed type or treatment with pre-diagnosis bleeding phenotype or post-diagnosis bleeding status.
[d]Oral contraceptive use was evaluated in female patients only.
[e]Only one patient (who had no claim for epistaxis) after diagnosis had nasal cauterization.

Except for joint bleeds, occurrence of all bleed types before diagnosis was more frequent among both male and female patients who continued to bleed post-diagnosis than among those whose bleeding resolved (Figure 3A, 3B). The differences were statistically significant among men and women combined for GI bleeding, epistaxis, HMB and coagulation defects complicating pregnancy, childbirth or the puerperium (Table 2). Pre-diagnosis GI bleeds, HMB and epistaxis were significant predictors of continued bleeding post-diagnosis (Table 3).

3.6 | Treatments

Overall, 19.4% of patients had treatment claims associated with VWD in the pre-diagnosis period, increasing to 27.1% of patients post-diagnosis. Use of oral contraceptives (OCs), but not other treatments, before diagnosis was significantly more common among those with multiple (vs single) bleed sites (Table 2), and the use of OCs and nasal cauterization before diagnosis was significantly associated with multiple-site bleeding (Table 3). Following diagnosis, use of OCs, desmopressin and aminocaproic acid (ACA) was significantly more common among patients with multiple (vs single) bleed sites before diagnosis (Table 2), and use of desmopressin and ACA post-diagnosis was significantly associated with pre-diagnosis multiple-site bleeding (Table 3).

In women with resolved bleeding, the most common pre-diagnosis treatment claims were for OCs, desmopressin and nasal cauterization, compared with OCs, desmopressin and ACA in the post-diagnosis period (Figure 4A). In women with continued bleeding, most pre- and post-diagnosis claims were for OCs, desmopressin and ACA (Figure 4B). Among men with resolved bleeding, desmopressin, ACA and nasal cauterization were the most common pre-diagnosis treatments, compared with desmopressin, ACA and von Willebrand factor (VWF) in the post-diagnosis period (Figure 4A). In men with continued bleeding, the most common pre-diagnosis treatments were nasal cauterization,

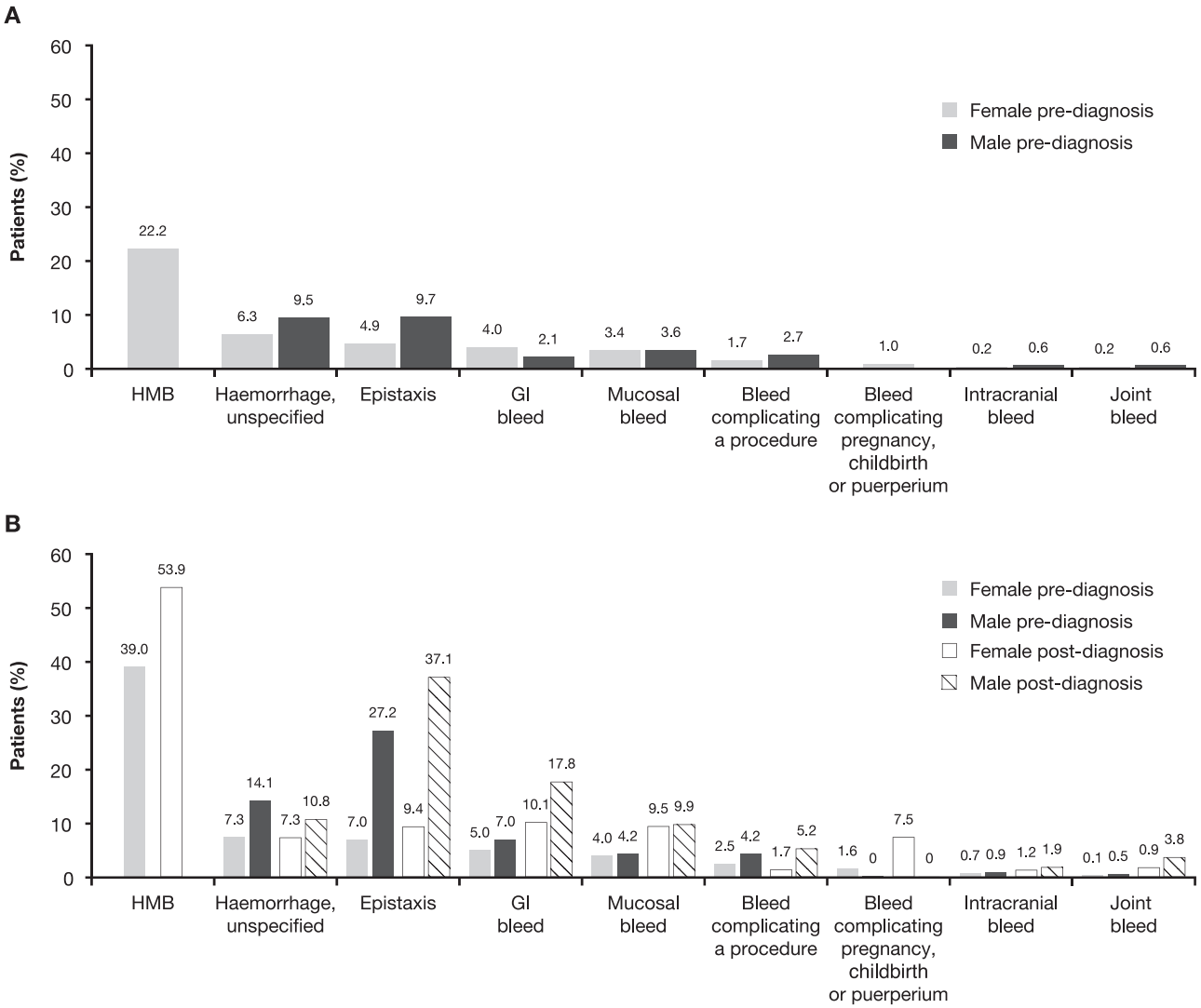

FIGURE 3 Most common bleed types for bleed claims. (A) Patients with resolved bleeding. (B) Patients with continued bleeding. GI, gastrointestinal; HMB, heavy menstrual bleeding.
Data are percentage of patients with a bleed claim for the bleed type. In addition, claims for 'post-partum bleeds' were submitted for .5% of female patients with resolved bleeding and for .6% (pre-diagnosis) and 1.1% (post-diagnosis) of those with continued bleeding

desmopressin and ACA, compared with ACA, desmopressin and nasal cauterization post-diagnosis (Figure 4B). Among all patients with continued bleeding, the proportion of treatment claims for VWF increased at least fourfold from the pre- to post-diagnosis period (Figure 4B).

Compared with patients whose bleeding resolved, those with continued bleeding had significantly greater pre-diagnosis use of OCs and nasal cauterization (Table 2); and use (vs non-use) of OCs, ACA and nasal cauterization pre-diagnosis were significant predictors of continued bleeding post-diagnosis (Table 3). After diagnosis, all treatment types were used in significantly more patients with continued bleeding compared with resolved bleeding (Table 2), and all were significantly associated with continued bleeding in regression analysis (Table 3).

Post-diagnosis use of each evaluated treatment type was significantly associated with at least one post-diagnosis bleed type: namely, OCs with GI bleeding and HMB; desmopressin with HMB and epistaxis; VWF with GI bleeding, coagulation defects complicating pregnancy, childbirth or the puerperium, and haemorrhage unspecified; and ACA with epistaxis and haemorrhage unspecified (Table 4).

4 | DISCUSSION

This analysis of medical claims data indicated that many patients with VWD continue to have bleeding events after diagnosis. Patients who continued to have bleeds were predominantly female and appeared to differ from those in whom bleeding resolved in several ways, suggestive of a unique bleeding phenotype: they were diagnosed at a younger age, and were more likely to have seen a haematologist, had claims for anaemia, and had bleed claims in the 18 months before diagnosis

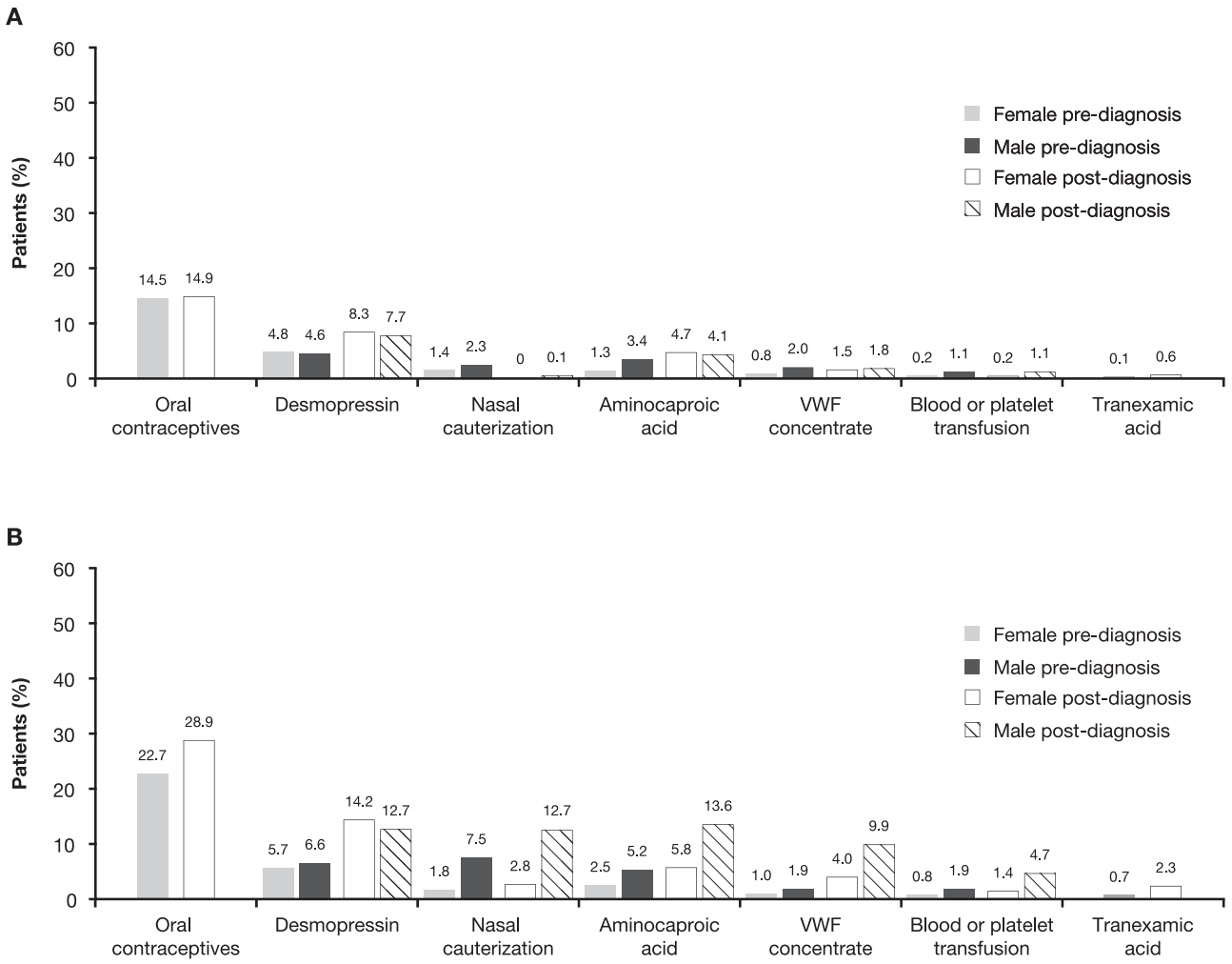

FIGURE 4 VWD-associated treatment claims. (A) Patients with resolved bleeding. (B) Patients with continued bleeding. VWD, von Willebrand disease; VWF, von Willebrand factor

(particularly for GI bleeding, HMB or epistaxis). Although GI bleeding and HMB are relatively common among patients with VWD, they can be particularly difficult to treat regardless of diagnosis; identification of a successful clinical strategy to prevent or treat patients' bleed events may be prolonged due to the paucity of data supporting effective management strategies.[14–16] Patients with continued bleeding were more likely than those with resolved bleeding to have received OCs, ACA or nasal cauterization before diagnosis, reflecting the common bleed types.

Following diagnosis, the proportion of patients with bleed claims for HMB, epistaxis, and particularly GI bleeding increased among those with continued bleeding, suggestive of greater recognition of bleeding events. GI bleeding in VWD may be recurrent, accounts for most VWD-related hospitalizations and is overrepresented in young, black and male patients.[21–24] In this analysis, among patients with continued bleeding we also observed a higher proportion of male (compared with female) patients with claims for GI bleeding. As might be expected given the increase in bleeding claims post-diagnosis, claims for most treatment types increased following diagnosis in patients with continued bleeding. This was most notable for VWF in men, probably reflective of the large increase in claims for GI bleeding in male patients. Overall, post-diagnosis VWF treatment was significantly associated with GI bleeding; OCs with GI bleeding and HMB; desmopressin with HMB and epistaxis; and ACA with epistaxis. While these treatment patterns are consistent with current treatment approaches by bleeding type, these data suggest an opportunity to further tailor treatment in VWD to reduce bleeding events after diagnosis.

Hospitalists, OBGYNs and PCPs were identified as the most common treating physicians both pre- and post-diagnosis; this was despite a post-diagnosis increase in claims for bleed types and treatments for which a haematologist referral might be expected in patients with persistent bleeding. In fact, haematologist visits for bleeding management were documented for only 8% of patients with continued bleeding after diagnosis. Some haematologists may have been categorized as hospitalists, but nevertheless the data highlight an opportunity to increase rates of referral to haematologists and for educational efforts

TABLE 4 Association of post-diagnosis treatment with post-diagnosis presenting bleed type

	GI (vs no GI) bleeding		HMB (vs no HMB)		Mucosal (vs no mucosal) bleeding		Epistaxis (vs no epistaxis)		Coagulation defects complicating pregnancy, childbirth, or puerperium (vs none)		Haemorrhage unspecified (vs no haemorrhage unspecified)	
	Odds ratio (95% CI)[a]	*P*	Odds ratio (95% CI)[a]	*P*	Odds ratio (95% CI)[a]	*P*	Odds ratio (95% CI)[a]	*P*	Odds ratio (95% CI)[a]	*P*	Odds ratio (95% CI)[a]	*P*
Oral contraceptives[b]	1.883 (1.14–3.11)	.0134[b]	3.53 (2.84–4.39)	<.0001[c]	1.22 (.69–2.14)	.492	.69 (.40-1.17)	.1686	1.21 (.72–2.04)	.4734	1.02 (.57–1.84)	.9503
Desmopressin	1.147 (.65–2.03)	.6378	1.63 (1.24–2.14)	.0004[c]	1.42 (.81-2.48)	.22	1.71 (1.12–2.60)	.013[c]	.95 (.47–1.93)	.8908	1.06(.56–2.01)	.8584
Von Willebrand factor	3.09 (1.56–6.16)	.0013[b]	1.48 (.86–2.53)	.1575	1.31 (.47–3.62)	.61	1.55 (.74–3.26)	.2499	3.76 (1.66-8.53)	.0015[c]	2.74 (1.23-6.09)	.0133[c]
Aminocaproic acid	1.48 (.70-3.11)	.3036	.91 (.61–1.37)	.6665	1.16 (.50-2.71)	.7266	2.65 (1.66–4.22)	<.0001[c]	.42 (.10-1.72)	.2253	2.57 (1.63-4.85)	.0036[c]
Nasal cauterization	2.42 (.94-6.27)	.0685	1.50 (.65–3.44)	.3419	1.20 (.29–5.02)	.8017	>999.99 (225 to > 999)	<.0001[c,d]	<.001 (< .001 to > 999)	.915	2.13 (.65-6.97)	.2133

CI, confidence interval.

Multiple logistic regression analysis with age (exact), sex and haematologist visit history as control variables.

[a]If OR = 1, there is an equal likelihood of the bleed type or lack of; if OR > 1, the bleed type is more likely than lack of, and if OR < 1, the bleed type is more likely to be lacking than present.

[b]Oral contraceptive use was evaluated in female patients only.

[c]Significant association between post-diagnosis treatment and post-diagnosis bleed type.

[d]Only one patient (who had no claim for epistaxis) after diagnosis had nasal cauterization.

directed at non-haematologists on unmet needs in VWD management, including the importance of referral to haemophilia treatment centres (HTCs).[9,10] Our findings could help providers involved in diagnosing VWD to identify patients with a potentially more severe bleeding phenotype and increased risk of continued bleeding, who may be most in need of coagulation-specialist haematology care.

Around one in five patients had bleed claims for multiple bleed sites in the 18 months before diagnosis, indicative of an elevated bleeding tendency demonstrated across multiple anatomic locations. While we did not perform a cluster analysis, patients with multiple-site bleeding patterns were more likely to have HMB and coagulation defects complicating pregnancy, childbirth or puerperium, and had a tendency towards epistaxis. Further, patients with continued bleeding after diagnosis were more likely than those with resolved bleeding to have GI bleeding, HMB and epistaxis prior to diagnosis, highlighting the severity of this bleeding phenotype. Our study underscores the continued need for both improved diagnosis and treatment, consistent with the known association between the number of bleeding symptoms and increasing odds of VWD diagnosis.[25]

HMB appears to be a common component of a multiple-site (and potentially more severe) bleeding phenotype. Non-haematology specialists, including PCPs or OBGYN physicians, may not always recognize HMB alone as unusual, particularly given the high rate of HMB in the general population and of anovulatory bleeding in young women[9]; it may be that a bleeding disorder is only suspected and diagnosed when other symptoms occur. Previous studies have highlighted a long delay in diagnosis of VWD among girls and women with HMB.[26,27] Although the American College of Obstetricians and Gynecologists Committee Opinion on the management of women with VWD recommends further evaluation in cases of excessive menstrual bleeding since menarche,[28] there is evidence that this may not occur routinely,[29,30] perhaps relating to a lack of awareness of the role of HTCs in co-management of excessive menstrual bleeding in VWD.[27,31]

Two treatment-related findings in the current analysis warrant further explanation. First, 4–7% of patients had claims for desmopressin apparently before VWD diagnosis. This may reflect desmopressin challenge tests performed between the first and second VWD insurance claims, or patients who already had a confirmed diagnosis for which they were receiving treatment (although prior diagnoses may be unlikely, given that patients were required to be continuously enrolled in the analysis database for 2 years prior to the first VWD claim code). The pre-diagnosis claims for desmopressin could also reflect empirical treatment in advance of obtaining a formal VWD diagnosis, as might be expected for paediatric or geographically remote patients who have laboratory results potentially indicative of low VWF or mild VWD. Second, some patients with resolved bleeding had haemostatic treatment claims after diagnosis. This may reflect claims made for various purposes, including for prophylactic treatment (although long-term prophylactic desmopressin use would not be expected); for medication kept at home as a precaution only; or for prescriptions obtained at maintenance visits by patients with mild intermittent bleeding symptoms for which specific bleed claims were not made.

Our findings are limited by the source database coverage and, as such, cannot be extrapolated beyond the US commercially insured VWD population. Further, as the database-enrolled population is generally representative of the under 65-year-old commercially insured population, the findings may be less applicable to older adults with VWD. In addition, the analysis was based on ICD-9 coding, which provides no information on VWD type or severity and only limited information on bleed type. As bleeding severity and phenotype are influenced by VWD type and subtype,[6–8] exploring the relationship between VWD type and continued vs resolved bleeding following diagnosis or multiple- vs single-site bleeding could further enhance understanding of bleeding patterns in VWD.[6] Information on treating physician specialty was also limited, particularly in relation to 'hospitalists', which may have included some haematologists. The accuracy of the database coding is also unknown, although the eligibility requirements should minimize the potential for inclusion of patients who did not have VWD.

5 | CONCLUSIONS

This claims analysis provides evidence that many patients with VWD bleed from multiple sites and/or continue to experience significant bleeding events after diagnosis yet are primarily treated by non-haematologists. Clinical factors associated with these challenging bleeding patterns are also identified. The findings highlight unmet needs in the treatment and management of VWD and the importance of optimizing and personalizing individual treatment through coagulation-specialist haematology care at HTCs.

ACKNOWLEDGEMENTS

This research was funded by Baxalta US Inc., a member of the Takeda group of companies, Lexington, MA, USA. Data were obtained from the IQVIA PharMetrics Plus database. Analyses were undertaken by Charles River Associates, Boston, MA, including Imrran Halari and was funded by Baxalta US Inc., a member of the Takeda group of companies, Lexington, MA, USA. Medical writing support was provided by Mary Berrington, PhD, and Iain Patefield, MS, of Parexel, Hackensack, NJ, USA, and was funded by Baxalta US Inc., a member of the Takeda group of companies, Lexington, MA, USA.

CONFLICTS OF INTEREST

JCR has acted as a paid consultant for CSL Behring, Hema Biologics, Takeda, Sanofi Genzyme, Novo Nordisk, Octapharma, Pfizer, Spark and uniQure; is on speaker bureaus for Takeda, Sanofi Genzyme, Novo Nordisk and Octapharma; and has received funding for research from Takeda not related to this study. LMM has received research funding from Bioverativ and consulting fees from Takeda, Spark, Sanofi Genzyme, Bayer, Hema biologics and CSL. IH is a current employee of Charles River Associates. SAH is an employee of Baxalta US Inc., a Takeda company and holds stock and/or stock options in Takeda. AO was an employee of Baxalta US Inc., a Takeda company at the time of

the study and owns Takeda stock. RFS has acted as a paid consultant to Takeda and Octapharma and has received an investigator-initiated grant from Takeda for the ATHN 9 study (natural history study in severe VWD).

AUTHOR CONTRIBUTIONS

SAH and AO conceived the analysis proposal, which was then discussed and refined with JCR, LMM and RFS. IH extracted and analysed the medical claims data. All authors were involved in data interpretation and determining the focus and content of the publication. All authors reviewed and commented on manuscript drafts and approved the final draft for publication.

DATA AVAILABILITY STATEMENT

Takeda does not plan to share data supporting the results reported in this article. The datasets reported in this this analysis are the property of IQVIA, and as such the authors and sponsors of this manuscript are unable to provide access to the raw data.

ORCID

Jonathan C. Roberts https://orcid.org/0000-0002-9415-9543
Lynn M. Malec https://orcid.org/0000-0001-9173-7179
Sarah A. Hale https://orcid.org/0000-0002-5227-0673
Robert F. Sidonio Jr https://orcid.org/0000-0002-9509-9415

REFERENCES

1. Sharma Ruchika, Haberichter SandraL. New advances in the diagnosis of von Willebrand disease. *Hematology Am Soc Hematol Educ Program*. 2019;2019:596-600.
2. Heijdra JessicaM, Cnossen MarjonH, Leebeek FrankWG. Current and emerging options for the management of inherited von Willebrand disease. *Drugs*. 2017;77:1531-1547.
3. Ng Christopher, Motto DavidG, Di Paola Jorge. Diagnostic approach to von Willebrand disease. *Blood*. 2015;125:2029-2037.
4. Bowman M, Hopman WM, Rapson D, Lillicrap D, James P. The prevalence of symptomatic von Willebrand disease in primary care practice. *J Thromb Haemost*. 2010;8:213-216.
5. Schinco P, Castaman G, Coppola A, et al. Current challenges in the diagnosis and management of patients with inherited von Willebrand's disease in Italy: an Expert Meeting Report on the diagnosis and surgical and secondary long-term prophylaxis. *Blood Transfus*. 2018;16:371-381.
6. Tosetto Alberto, Badiee Zahra, Baghaipour Mohammad-Reza, et al. Bleeding symptoms in patients diagnosed as type 3 von Willebrand disease: results from 3WINTERS-IPS, an international and collaborative cross-sectional study. *J Thromb Haemost*. 2020;18:2145-2154.
7. Castaman G, Federici AB, Tosetto A, et al. Different bleeding risk in type 2 A and 2 M von Willebrand disease: a 2-year prospective study in 107 patients. *J Thromb Haemost*. 2012;10:632-638.
8. Nichols WL, Hultin MB, James AH, et al. von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). *Haemophilia*. 2008;14:171-232.
9. Zia A, Lau M, Journeycake J, et al. Developing a multidisciplinary Young Women's Blood Disorders Program: a single-centre approach with guidance for other centres. *Haemophilia*. 2016;22:199-207.
10. The Lewin Group for the National Hemophilia Foundation. Strategic Summit on Von Willebrand Disease. https://www.hemophilia.org/sites/default/files/document/files/NHF-Strategic-Summit-Report-on-von-Willebrand-disease_1.pdf. Accessed September 9, 2020.
11. Roberts JC, Flood VH. Laboratory diagnosis of von Willebrand disease. *Int J Lab Hematol*. 2015;37(Suppl 1):11-17.
12. Roberts JonathanC, Morateck PattiA, Christopherson PamelaA, et al. Rapid discrimination of the phenotypic variants of von Willebrand disease. *Blood*. 2016;127:2472-2480.
13. Sidonio Jr RobertF, Zia Ayesha, Fallaize Dana. Potential undiagnosed VWD or other mucocutaneous bleeding disorder cases estimated from private medical insurance claims. *J Blood Med*. 2020;11:1-11.
14. Leebeek FrankWG, Eikenboom JeroenCJ. Von Willebrand's disease. *N Engl J Med*. 2016;375:2067-2080.
15. Ragni MV, Machin N, Malec LM, et al. Von Willebrand factor for menorrhagia: a survey and literature review. *Haemophilia*. 2016;22:397-402.
16. Peyvandi F, Castaman G, Gresele P, et al. A phase III study comparing secondary long-term prophylaxis versus on-demand treatment with vWF/FVIII concentrates in severe inherited von Willebrand disease. *Blood Transfus*. 2019;17:391-398.
17. Sidonio RF, Haley KM, Fallaize D. Impact of diagnosis of von Willebrand disease on patient outcomes: analysis of medical insurance claims data. *Haemophilia*. 2017;23:743-749.
18. Barr RonaldD, Sek Julia, Horsman John, et al. Health status and health-related quality of life associated with von Willebrand disease. *Am J Hematol*. 2003;73:108-114.
19. Rae C, Furlong W, Horsman J, et al. Bleeding disorders, menorrhagia and iron deficiency: impacts on health-related quality of life. *Haemophilia*. 2013;19:385-391.
20. Roberts JonathanC, Kulkarni Roshni, Kouides PeterA, et al. Healthcare utilization and health related quality of life in persons with von Willebrand disease. *Blood*. 2020;136:3-4.
21. Brown Racquel. Recombinant von Willebrand factor for severe gastrointestinal bleeding unresponsive to other treatments in a patient with type 2 A von Willebrand disease: a case report. *Blood Coagul Fibrinolysis*. 2017;28:570-575.
22. Holm E, Carlsson KSteen, Lövdahl S, Lail AE, Abshire TC, Berntorp E. Bleeding-related hospitalization in patients with von Willebrand disease and the impact of prophylaxis: results from national registers in Sweden compared with normal controls and participants in the von Willebrand Disease Prophylaxis Network. *Haemophilia*. 2018;24:628-633.
23. Liao Li-Chin, Liao Szu-Chia, Chang Chung-Hsin, Shih Ming-Yang, Wang Jiaan-Der. Gastrointestinal angiodysplasia in two patients with type 3 von Willebrand disease. *Blood Coagul Fibrinolysis*. 2019;30:243-245.
24. Tsagianni Anastasia, Comer DianeM, Yabes JonathanG, Ragni MargaretV. Von Willebrand disease and gastrointestinal bleeding: a national inpatient sample study. *Thromb Res*. 2019;178:119-123.
25. Spradbrow Jordan, Letourneau Sasha, Grabell Julie, et al. Bleeding assessment tools to predict von Willebrand disease: utility of individual bleeding symptoms. *Res Pract Thromb Haemost*. 2020;4:92-99.
26. Ragni, Bontempo, Hassett ACortese. von Willebrand disease and bleeding in women. *Haemophilia*. 1999;5:313-317.
27. Kirtava A, Crudder S, Dilley A, Lally C, Evatt B. Trends in clinical management of women with von Willebrand disease: a survey of 75 women enrolled in haemophilia treatment centres in the United States. *Haemophilia*. 2004;10:158-161.
28. American College of Obstetricians and Gynecologists. Committee opinion on von Willebrand disease in women. No 580. https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2013/12/von-willebrand-disease-in-women. Accessed January 31, 2020.
29. Byams VanessaR, Anderson BrittaL, Grant AltheaM, Atrash Hani, Schulkin Jay. Evaluation of bleeding disorders in women with menorrhagia: a survey of obstetrician-gynecologists. *Am J Obstet Gynecol*. 2012;207:269 e261-265.

30. Khamees Deena, Klima Jennifer, O'brien SarahH. Population screening for von Willebrand disease in adolescents with heavy menstrual bleeding. *J Pediatr*. 2015;166:195-197.
31. Haley KristinaM, Sidonio RobertF, Abraham Shirley, Cheng Dunlei, Recht Michael, Kulkarni Roshni. A cross-sectional study of women and girls with congenital bleeding disorders: the American thrombosis and hemostasis network cohort. *J Womens Health (Larchmt)*. 2020;29:670-676.

How to cite this article: Roberts JC, Malec LM, Halari I, Hale SA, Oladapo A, Sidonio RF. Bleeding patterns in patients before and after diagnosis of von Willebrand disease: Analysis of a US medical claims database. *Haemophilia*. 2022;28:97–108. https://doi.org/10.1111/hae.14448